APPENDIX C: RISK FACTORS FOR CHILDHOOD CANCER

Childhood Cancer In General

The term cancer is used to describe a variety of diseases associated with abnormal cell and tissue growth. These different diseases are classified by primary site (location in the body where the disease originated) and the histology or cell type (determined under a microscope). Epidemiologic studies have revealed that different histologic types of cancer are individual diseases with separate causes, risks, characteristics and patterns of survival (Schottenfeld and Fraumeni 1996).

Cancer is relatively rare in children. Of approximately 1 million cases of cancer diagnosed yearly in the United States, about 7,500 affect children (Bleyer 1990, Miller et al 1993). Despite improved therapy (Young et al 1986, Miller et al 1993), cancer is second only to accidents among the leading causes of mortality in children ages 0-14 in the United States (Chow et al 1996).

Causes suggested for childhood cancers vary by the specific type of cancer being considered. However, past research has suggested risk factors including genetic factors, prenatal exposures, exposure to viral infections, exposure to pesticides, exposure to ionizing and non-ionizing radiation, parental occupation exposures to petrochemicals, hydrocarbons, metals and pesticides, and medical exposures including prenatal x-rays, chemotherapy, and other medications (Chow et al 1996). The discussion below includes information on possible risk factors for some of the more common childhood cancers.

The most common childhood cancers in the United States are cancers of the blood and lymph systems, called leukemias and lymphomas. Leukemia accounts for about one third of all childhood cancers. Other cancers that are common in children include cancers of the brain, bone, soft tissues, and kidney.

Leukemia

Leukemia is a group of malignancies arising from the blood forming cells of the bone marrow, classified as separate histological types.

There are four major subtypes into which most histologic types of leukemia can be categorized: acute lymphoid leukemia (ALL); acute myeloid leukemia (AML); chronic myeloid leukemia (CML); and chronic lymphoid leukemia (CLL). Epidemiologic studies have shown that each histologic type of leukemia is an individual disease with specific characteristics, patterns of survival, and etiologic factors. While there are known and suspected risk factors for each subtype, leukemia cases are relatively rare, and despite a large body of research, risk factors that have been identified for different leukemia subtypes only account for a small percentage of cases. Clusters of leukemia have been noted and intensely investigated but environmental links were rarely found (for example, see Woburn Childhood Leukemia Follow-Up Study by the Massachusetts Department of Public Health, 1997).

Acute Lymphoid Leukemia

Acute lymphoid leukemia (ALL) occurs predominantly in children (ACS 1995). Acute lymphocytic leukemia differs from most other cancers in that there is a peak in leukemia incidence among children of 1 to 4 years of age (Linet, 1985). Leukemia occurring in children under 7 years of age is a disease distinct from that affecting older children and adults. The known risk factors for ALL are exposures to ionizing radiation or to benzene. Suspected risk factors are genetic, viral, environmental, and occupational. Studies of associations between leukemia and chromosomal aberrations such as Down syndrome have related ALL to a genetic etiology (Scheinberg and Golde 1994). Other research has supported viral factors. An increased risk of childhood ALL has been associated with exposure to several chemicals and possible paternal occupational exposure to hydrocarbons (Linet 1985).

Acute Myeloid Leukemia

Although acute myeloid leukemia (AML) does affect children under ten, the incidence of AML increases after age 10, rising rapidly at age 50 and finally leveling off in the very elderly. The known risk factors for AML are similar to those for ALL: exposure to ionizing radiation or to benzene (Linet 1985). Current thinking based on recent studies suggests that viral and genetic factors play a less important role in the development of AML than in ALL and CLL. Suspected risk factors for AML include occupational and environmental exposures and certain drug therapies, such as chloramphenical and phenylbutazone (Linet 1985). Suspected chemical exposures include petroleum products and organic solvents.

Chronic Myeloid Leukemia

Of all the leukemias, Chronic myeloid leukemia (CML) is among the least understood. The risk factors for CML in children are unknown. Chronic lymphoid leukemia is chiefly an adult disease with 90 percent of cases occur in people over 50 years old (ACS 1990).

Lymphomas

Lymphomas are made up of several subtypes of disease with differing risk factors. Of particular concern to Cape Cod children are the subtypes Hodgkin. s Disease and non-Hodgkin. s Lymphoma.

Non-Hodgkin. s Lymphoma

There are many types of lymphoma. In the United States, the two most common types of lymphoma are Non-Hodgkin. s lymphoma (NHL) and Hodgkin. s disease (HD). Non-Hodgkin. s lymphoma (NHL) includes all lymphomas except Hodgkin. s disease. Incidence rates are higher in males than in females in all countries (Scherr and Mueller 1996). Researchers have found that the incidence of NHL has been markedly increasing over time (Schottenfeld and Fraumeni 1996).

NHL is more common among people who have abnormal or compromised immune systems due to inherited immunodeficiency diseases, organ transplant therapies, and autoimmune disorders. The Epstein-Barr virus has also been linked to increased risk of some types of NHL in the United States (Schottenfeld and Fraumeni 1996).

Ionizing radiation has been shown to induce lymphoma in laboratory animals. Exposure to ionizing radiation from the atomic bombs dropped on Japan was associated with an elevation of NHL in persons who were under 25 years of age at exposure. Exposures to some therapeutic radiation treatments have also been associated with the development of NHL (ACS 1996, Freedman and Hadler 1994, Shottenfeld and Fraumeni 1996).

Chemicals agents suspected of inducing lymphoma include phenoxy acids, chlorophenols, organic solvents, pesticides, and herbicides; however, a causal association in humans has not been established due to the inconsistency of study results (Higginson et al 1992).

Elevated risks of lymphoma have been found among children whose mothers smoked (John et al 1991, Schwartzbaum et al 1991).

Hodgkin's Disease

The incidence of Hodgkin. s disease is low before five years of age but increase by ages 10 to 14 years to equal the incidence of NHL. Disease incidence is higher in males than in females. The disease is less common among blacks than among whites in the United States (Chow et. al., 1996).

One study found an increase in risk for children residing near power lines (Olsen et al 1993), however other studies have not confirmed this finding (Chow et al 1996).

Infection with the Epstein-Barr virus (EBV) is considered a risk factor for Hodgkin. s disease in children (Bogger-Goren et al 1983, IRAC 1997), in part because children (younger than 15 years old) residing in poor living conditions are at higher risk of the disease (Mueller et al 1996). In addition, almost all children who were diagnosed with Hodgkin. s disease under the age of 10 were positive for EBV infection (Razzouuk et al. 1997). The timing of infection with the virus is believed to have an affect on the risk of developing Hodgkin. s disease since researchers have found that the risk of HD in the United States is lower for older children (15 years or older) who have a larger number of siblings, a later birth order or who reside in multiple-family homes (Gutensohn and Cole 1981, Mueller et al 1996). EBV is an extremely common infection, which only causes cancer under unusual conditions. There is no danger of transmitting an EBV-associated cancer between people.

A peak of Hodgkin. s disease in early adulthood is not unexpected if an infectious agent was being transmitted between children of school age. It is important to emphasize that according to the hypothesis exposure to the infectious agent only rarely results in a diagnosis of Hodgkin. s disease. Other steps in the causal pathway would have to be fulfilled for a cancer to develop unchecked. The distribution of age at diagnosis and histological cell type is similar to that proposed by this hypothesis in that one half of the Hodgkin. s disease cases on Cape Cod were diagnosed to children over 14 years of age.

Clusters of diagnoses of Hodgkin. s disease have been noted however, links with environmental risk factors have been difficult to identify.

Central Nervous System Tumors

Central nervous system (CNS) tumors are the most common childhood cancer after the leukemias and lymphomas (Parkin et al., 1988b). Male to female differences are smaller than for lymphoma or leukemia ratios, generally ranging from 0.9 to 1.3 males diagnosed for each diagnosis among females.

Central nervous system tumors include brain cancers and other nervous tissue cancers. CNS tumors in children are different histological types (look different under the microscope) than are cancers at the same anatomical sites in adults. The most common types of CNS tumors that affect children are gliomas including astrocytomas and ependymomas, as well as medulloblastomas (Chow et al. 1996).

Little is known about the causes of brain cancer. Epidemiologic studies have linked the incidence of brain cancer with genetic, environmental, and occupational factors. Some studies have noted a genetic pattern or familial tendency to develop gliomas (Farwell and Flannery 1984, Mauron et al 1984, Salcman and Soloman 1984). Most studies of brain and CNS tumors in children focus on either direct exposure to children or on exposure from parental exposure to occupational sources.

Some of the exposures occurring directly to children occur prenatally. For example, children who were exposed in utero to sodium nitrate meat preservative were found to have an increased risk of brain tumors (Preston-Martin et al 1982, Preston-Martin and Henderson 1984, Kuijten et al 1990, Bunin et al 1994, McCredie et al 1994a, Sarasua and Savitz, 1994). Exposure to barbiturates in utero increased the risk of developing brain tumors in childhood (Page and Asire 1985). However, exposures during childhood are also hypothesized to be risk factors for CNS tumors. Children who were treated with barbiturates during childhood have been found to be at increased risk for brain tumors (Goldhaber et al 1990, Page and Asire 1985). The incidence of brain tumors was found to be higher in children exposed to insecticides in some studies (Gold et al 1979), but not all (Schwartzbaum et al 1991). Elevated risks of brain cancer are suspected to be due to maternal smoking (Filippini et al 1994). Exposure to high dose x-rays is known to be a risk factor for brain cancer. Children irradiated with large doses of x-rays as a treatment for ringworm were found to have four times as many head and neck cancers (brain, parotid and

thyroid cancers) as expected (Modan et al 1974). Other studies have shown increased risk of brain tumors in children radiated for treatment of leukemia (Jankovic et al 1991).

Children whose fathers were potentially exposed to large amounts of non-ionizing electromagnetic field radiation at work were found to have higher rates of childhood brain cancer (Wilkins and Sinks 1990) and nervous system cancers (Spitz and Johnson 1985, Johnson and Spitz 1989). Not all authors have found these associations however (Nasca et al. 1988, Bunin et al 1990). Since carcinogenic exposure in the last trimester of pregnancy is suspected to be related to childhood brain and CNS tumors, study of small parental exposure during the course of pregnancy is very important. However, there are a number of methodological difficulties in conducting this type of study, particularly the lack of specific information on exposure in parents and whether exposure at work actually results in exposure to children in the home.

Renal Tumors

Kidney tumors involve renal cell cancers (the main area of the kidney), renal pelvis cancers (lower kidney area which collects urine), ureter cancers (tube conducting urine from kidney to the bladder) and urethera cancers (leading from the bladder and discharging urine) (ACS 1996). The most common kidney type among children is Wilms. tumor, a tumor of embryonal kidney cells (Parkin et al 1988a, Stiller and Parkin, 1990). The highest rates of this tumor in the world are observed among blacks in the United States. Females have a slightly higher rate of kidney cancer than males in all ethnic groups (Breslow et al 1994).

Some studies, but not all, have found an increase in the risk of Wilms. tumor after prenatal exposure to radiation (Chow et al 1996). Exposure to pesticides have been linked to Wilms. tumor by one study (Olshan et al 1993). Children exposed to a viral infection in utero were found to be at increased risk of developing Wilms. tumor by some authors (Bunin et al 1987), but not by others (Birch et al 1990, Giuffre et al 1990 and others). Children of fathers who worked in lead related occupations were also found to have a higher risk of developing Wilms. tumor (Kantor et al 1979, Olsen et al 1991, Bunin et al 1989) in some studies but not all (Wilkins and Sinks 1984 a, b). However, many occupations with exposures to lead also have exposures to hydrocarbons, particularly to benzene. As with studies of parental occupation and brain cancer risk in children, the lack of specific information on exposure in parents and whether exposure at work actually results in exposure to children in the home hindered these studies.